DEPARTMENT OF HEALTH & HUMAN SERVICES

HFA-305

Food and Drug Administration
Rockville MD 20857

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Stephen R. Auten, Esq.
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Sandoz, Inc.
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Re: Docket No. FDA-2010-P-0087

Dear Mr. Auten:

This responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Sandoz, Inc. (Sandoz), on February 12, 2010. In the petition, Sandoz requests that FDA refrain from granting tentative or final approval for any abbreviated new drug application (ANDA) for a generic version of LYRICA (pregabalin) capsules if the ANDA includes proposed labeling that omits or carves out either LYRICA's seizure indication or LYRICA's pain indications. The petition contends that an ANDA that carves out the seizure indication for pregabalin must necessarily omit from the labeling essential information related to the risk of suicidal thoughts or behavior. Similarly, the petition contends that an ANDA that carves out the pain indications must omit from the labeling essential information related to the risk of peripheral edema. In the absence of either set of warnings, the petition maintains that the product would be less safe than the reference listed drug (RLD), LYRICA, for the remaining approved indications.

We have carefully reviewed the arguments in your petition. For the reasons stated below, we deny your request. In accordance with the Federal Food, Drug, and Cosmetic Act (the Act), FDA regulations, and case law, the Agency may approve an ANDA for a pregabalin product whose labeling omits or carves out either the seizure indication or the pain-related indications for which the RLD is approved.

I. BACKGROUND

A. LYRICA

On December 30, 2004, FDA approved two new drug applications (NDAs) (held by Pfizer Inc. and its wholly owned subsidiary, CP Pharmaceuticals International C.V.) for LYRICA (pregabalin) capsules (NDA 21-446 and 21-723). The NDAs were approved for management of neuropathic pain associated with diabetic peripheral neuropathy and management of postherpetic neuralgia, respectively. On June 10, 2005, FDA approved a third NDA (21-724) for LYRICA capsules as adjunctive therapy for adult patients with partial onset seizures (seizure indication). On June 21, 2007, FDA approved a

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supplement to NDA 21-446 for management of fibromyalgia.

The three pain-related indications (neuropathic pain, postherpetic neuralgia, and fibromyalgia) are all listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as claimed by U.S. Patent No. 6,001,876 (the '876 patent), with Use-Codes U-55 for "treatment of pain" and U-819 for "treatment of fibromyalgia." The '876 patent expires on December 30, 2018. The seizure indication is listed in the Orange Book as claimed by U.S. Patent No. 5,563,175 (the '175 patent) with Use Code U-661, "treatment of seizure disorders." The '175 patent expires on October 8, 2013.

B. The Statutory and Regulatory Basis for Labeling Differences Between ANDAs and NDAs on the Basis of Patent Claims

Before addressing the arguments you make in your petition, it is appropriate to summarize the statutory and regulatory provisions relevant to the approval of a generic drug product whose labeling omits an indication that is protected by a patent.

The Act and FDA regulations require that an entity seeking to market a new drug submit an NDA or ANDA. NDAs are submitted under section 505(b)(1) of the Act[1] and approved under section 505(c) of the Act. NDAs contain, among other components, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication or indications for which approval is sought. The Act and FDA regulations also require that an NDA applicant submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[2] FDA is required to publish patent information for drugs approved under section 505(c) of the Act and does so in the Orange Book (sections 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) or 505(j) is known as a *listed drug*.[3] Under provisions added to the Act by the 1984 Drug Price Competition and

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[1] Section 505 of the Act appears in the United States Code at 21 U.S.C. 355.

[2] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[3] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is

Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic[4] versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, and route of administration) and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of an ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[5] In general, an ANDA may not obtain final approval until listed patents submitted before the ANDA submission and marketing exclusivity for the listed drug have expired or until the NDA holder and patent owner(s) for the relevant patents have had the opportunity to defend their patent rights in court.

Specifically, with respect to each patent submitted by the NDA applicant for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) That the required patent information relating to such patent has not been filed (paragraph I certification)
(II) That such patent has expired (paragraph II certification)
(III) That the patent will expire on a particular date (paragraph III certification)
(IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification)

One purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of

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identified as having an effective approval in the Orange Book, which includes any patent information that has been submitted for each approved drug (21 CFR 314.53(e)).

[4] Although the term *generic* is not defined in the Act or FDA's regulations, it is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[5] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity or enforceability of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(3) and (j)(2)(B) of the Act).

The submission of an ANDA or 505(b)(2) application for a drug claimed in a patent or the use of which is claimed in a patent with the purpose of obtaining approval prior to patent expiration (i.e., submitting such an application with a paragraph IV certification) is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). For those patents listed in the Orange Book at the time of the original submission of the ANDA, if the patent owner or NDA holder brings a patent infringement lawsuit against the ANDA applicant within 45 days of the date the notice of the paragraph IV certification is received, the approval of the ANDA will be stayed. The stay will be for 30 months from the date the notice of the paragraph IV certification was received unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval after the 45 days expire.

These paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents. An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii statement* acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit the protected use from its labeling (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii

statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[6]

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states the following:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[7]

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent and, therefore, need not seek approval for that use.[8]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac*

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[6] The Agency's interpretation of the plain language of the Act is further supported by congressional intent as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

[7] FDA regulations implementing this statutory provision use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[8] See also the final rule titled *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed* (68 FR 36676 (June 18, 2003)). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated: "Our position has been that, for an ANDA applicant to file a section viii statement, it must 'carve out' from the proposed ANDA labeling, the labeling protected by the listed patent" (Id.).

Pharmaceutical Company v. Thompson, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (Id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent and, under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all patents listed at the time the ANDA was submitted (1) have expired, (2) have been successfully challenged, (3) have been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) have been subject to a paragraph IV certification that led to a lawsuit within 45 days and a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

C. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress' intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. In § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[9]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

[9] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* or accorded exclusivity under section 505(j)(4)(D) of the act [emphasis added]. [10]

The regulations at § 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent*" [emphasis added], we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use."

Case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer. Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is permissible as a change due to difference in manufacturer so long as the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. DISCUSSION

In your petition, you state that, based on publicly available court documents, you believe that there may be pending ANDAs seeking approval of a generic version of LYRICA that propose to carve out the seizure indication as well as other pending ANDAs that propose to carve out the three pain-related indications (Petition at 3). You state further that your

[10] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

ANDA, in contrast, does not include any section viii statements seeking to omit any indications for which LYRICA is approved. Rather, Sandoz has filed paragraph IV certifications to both the '175 and '876 patents (Petition at 2-3).

Your petition acknowledges that FDA has authority under the applicable statutes and regulations governing the approval of generic drugs to approve applications seeking to carve out patent-protected indications (Petition at 4). As noted, pursuant to § 314.127(a)(7), FDA may approve an ANDA with proposed carved out labeling if it finds that the differences in the labeling "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[11]

Your petition contends, however, that in the case of generic versions of LYRICA, approving ANDAs that seek to carve out the seizure or pain-related indications would be inappropriate, because such carve-outs would require the removal of necessary safety information from the labeling that would, in turn, render the product less safe than LYRICA for the remaining approved conditions of use, in contravention of § 314.127(a)(7). We disagree. As described below, we conclude that permitting carve-outs for certain patent-protected indications for pregabalin would not require removal of necessary warnings from the labeling and would not render the drug products less safe or less effective than LYRICA for the remaining conditions of use. Accordingly, your petition is denied.

A. Omission of the Seizure Indication from Pregabalin Labeling Would Not Render Pregabalin Less Safe or Effective for the Remaining Approved Conditions of Use.

In your petition, you argue that a proposed carve-out of LYRICA's seizure indication, which you say is claimed by the '175 patent, "would necessarily entail removal of section 5.4 of LYRICA's labeling, entitled 'Suicidal Behavior and Ideation,' in its entirety" because the section refers to LYRICA as an antiepileptic drug, thereby disclosing the patent-protected use (Petition at 4). You further argue that the increase in risk of suicidal thoughts or behavior applies to patients taking the drug for any indication and therefore the warning cannot be removed without rendering the product less safe than LYRICA for the remaining unprotected indications (Petition at 5). By this reasoning, you assert that

[11] On a number of occasions, we have affirmed our authority to approve ANDAs with carved-out labeling. For example, in our April 6, 2004, response concerning ribavirin, we affirmed our authority to approve ANDAs for ribavirin with labeling that omits protected information (April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1). We reiterated this position more recently in our March 13, 2008, response concerning ANDAs for amifostine with a protected indication carved out (March 13, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., Docket No. 2006P-0410/CP1); in our April 25, 2008, response concerning ANDAs for dronabinol (April 25, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Victor Raczkowski, M.D., Docket No. FDA-2007-P-0169); and in our June 18, 2008, response concerning ANDAs for ramipril (June 18, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Thomas K. Rogers, Docket No. FDA-2008-P-0304). In all cases, we determined that carved-out labeling would not render the products less safe or effective than the listed drug for the remaining approved indications of use.

FDA should not permit a carve-out of the patent-protected seizure indication because the necessary labeling carve-out would render the generic product less safe than LYRICA for the remaining unprotected pain indications.

We agree that the increased risk of suicidal thoughts and behavior applies to all patients taking pregabalin, regardless of the indication for which it is used. Section 5.4 of the LYRICA labeling is clear on this point, stating, "Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication." Therefore, FDA would require labeling for all pregabalin products to contain information about this risk.

Although we agree that the risk information conveyed in section 5.4 is necessary, we disagree that the entire section must be removed from the labeling of an ANDA approved with the seizure indication carved out. As discussed above, pursuant to § 314.94(a)(8)(iv), differences in the labeling of a generic drug product as compared to the RLD are permissible to prevent disclosure of aspects of the RLD labeling that are protected by patents or exclusivity. Such differences may include omissions of words or phrases from the RLD's labeling and minor attendant changes to ensure that the language of the labeling reads properly. The omissions need not be entire sections of the labeling that contain text disclosing a protected indication.

Section 5.4 of the LYRICA labeling mentions epilepsy and discusses LYRICA as an antiepileptic drug. It is our view that complete removal of section 5.4 is not necessary to ensure that the protected seizure indication is not disclosed. Rather, selective deletions and *de minimis* modifications in the labeling, consistent with § 314.94(a)(8)(iv), can adequately ensure that the necessary safety information is conveyed without disclosing the patent-protected indication. For example, in your petition, you cite the first paragraph of section 5.4 as disclosing a use that you say is claimed by the '175 patent and argue that the entire section should thereby be removed to avoid revealing the seizure indication (Petition at 5). The first paragraph of section 5.4 of the current LYRICA labeling reads as follows [12]:

> Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Contrary to your assertion, it is FDA's view that section 5.4 need not be deleted in its entirety to avoid disclosing the patent-protected indication. Instead, the above paragraph could be modified to read as follows:

> Pregabalin increases the risk of suicidal thoughts or behavior in patients taking

[12] The petition quotes language from the LYRICA labeling approved on April 23, 2009 (at 5). The current labeling, however, approved on January 5, 2010, contains minor revisions to section 5.4. This response addresses the language in section 5.4 of the current labeling.

> the drug for any indication. Monitor patients treated with pregabalin for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. [13]

As modified, the language reflects minor changes, consistent with § 314.94(a)(8)(iv), and adequately conveys the necessary safety information[14] without disclosing the patent-protected indication.

You additionally cite Table 2 in section 5.4 of the LYRICA labeling and the sentence following the table as disclosing the patent-protected seizure indication (Petition at 5). Table 2 is titled "Risk by indication for antiepileptic drugs in the pooled analysis" and presents risk data for "epilepsy," "psychiatric," and "other" indications. The sentence following Table 2 reads:

> The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

To avoid revealing the carved-out seizure indication, the title of Table 2 could be changed, for example,[15] to "Risk by indication for drugs in the pooled analysis." With respect to the mention of epilepsy in the table and the text following the table, in our view, this language does not disclose the patent-protected seizure indication. The discussion of epilepsy, in both cases, is in the context of a pooled analysis of 11 different drugs approved for seizure-related indications among a variety of other indications, including some for which pregabalin is not approved, such as psychiatric indications. The table does not refer specifically or exclusively to pregabalin. Therefore, in this context, the mention of "epilepsy," "psychiatric," and "other" conditions does not inappropriately reveal any indication for use. Accordingly, retaining this language in the labeling of a generic pregabalin product with the seizure indication carved out would not disclose a protected indication.

In addition to section 5.4 of the LYRICA labeling, you have also noted that the Medication Guide discusses LYRICA as an antiepileptic drug (Petition at 7). The

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[13] This language is intended simply as an example of modified language that FDA would find acceptable as conveying the necessary safety information without disclosing the protected indication. This is not intended to suggest that alternative proposed language in an ANDA seeking to carve out the indication might not also be acceptable.

[14] We note that in the example provided, the warning is no longer clearly stated as a class warning. The class warning is intended to convey that switching to another antiepileptic drug will not alleviate the increased risk of suicidal thoughts and behavior. The class nature of the warning becomes less significant when the drug is not approved for the class-related indication. In other words, if the product is not approved for the seizure indication and is only approved for pain-related indications, then from the perspective of patient safety, it is less important to convey that the risk of suicidal thoughts and behavior applies to all antiepileptic drugs. Rather, to protect patient safety, it is of primary importance to convey that the risk of suicidal thoughts and behavior applies to patients taking pregabalin.

[15] See supra n. 13.

relevant language in the Medication Guide reads as follows:

> 2. Like other antiepileptic drugs, LYRICA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
>
> Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:...

As discussed above, the warning about the increased risk of suicidal thoughts and behavior is necessary to ensure that generic pregabalin products are as safe as LYRICA for the remaining approved indications. Accordingly, FDA will require the suicide warning to be included in the Medication Guide of all approved pregabalin products. In the Agency's view, however, the information necessary to protect patient safety can adequately be conveyed without disclosing the carved-out seizure indication by making slight modifications to the language of the Medication Guide, consistent with § 314.94(a)(8)(iv). For example, the Medication Guide could read as follows:

> 2. Pregabalin may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
>
> Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:...

In this example, deleting a single phrase from the Medication Guide avoids revealing the carved-out seizure indication. The remaining language nonetheless conveys the same essential safety information to patients taking the drug.

B. Omission of the Pain Indications from Pregabalin Labeling Would Not Render Pregabalin Less Safe or Effective for the Remaining Approved Conditions of Use.

In your petition, you argue that a proposed carve-out for LYRICA's three pain indications that you say are claimed by the '876 patent (neuropathic pain, postherptic neuralgia, and fibromyalgia) would necessarily require the complete removal of section 5.5 of the LYRICA labeling entitled "Peripheral Edema" because the section mentions the use of LYRICA in studies of pain associated with diabetic peripheral neuropathy, thereby disclosing the use of pregabalin in treating pain. You further argue that the risk of peripheral edema applies to patients taking the drug for any indication and therefore the warning cannot be removed without rendering the product less safe than LYRICA for the remaining unprotected indications (Petition at 11-12). By this reasoning, you assert that FDA should not permit a carve-out of the patent-protected pain indications because removing section 5.5 in its entirety would render the generic product less safe than LYRICA for the remaining unprotected indications (Petition at 13).

We agree that the increased risk of peripheral edema applies to all patients taking pregabalin, regardless of the indication for which it is used. In fact, as you note in your petition, peripheral edema was observed as an adverse reaction in studies of adult patients

with partial onset seizures in addition to the pain studies (Petition at 12). Therefore, FDA will require labeling for all pregabalin products to contain information about this risk, regardless of the indications for which they are approved.

Although we agree that the warnings conveyed in section 5.5 are necessary, we do not agree that the entire section must be removed from the labeling of an ANDA approved with the pain-related indications carved out. Complete removal of section 5.5 is not necessary to ensure that the protected pain indications are not disclosed. As described below, the labeling, with minor modifications permitted under § 314.94(a)(8)(iv), can adequately convey the necessary safety information without disclosing the patent-protected pain indications.

In your petition, you specifically cite text from the third paragraph of section 5.5 as disclosing a use that you say is claimed by the '876 patent and argue that the entire warning should thereby be removed to avoid revealing the pain indications (Petition at 11). The sentence cited reads as follows:

> The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy.

Contrary to your assertion, it is FDA's view that section 5.5 need not be deleted in its entirety to avoid disclosing the patent-protected indications. Instead, minor modifications to the language in the section may be made to ensure that the safety information is conveyed without revealing the pain indications. For example, the above sentence could be modified to read as follows[16]:

> The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies examining diabetic patients.

As a further alternative, the entire sentence could be deleted from section 5.5. In both cases, the important risk information is still conveyed by section 5.5 to prescribing physicians without indicating that the drug may be useful in treating pain.

You also assert that information about the risk of peripheral edema must be removed from the Medication Guide, if the pain indications are carved out of the labeling, because the information is "primarily derived from clinical studies of LYRICA for treating pain." (Petition at 13). The language at issue in the Medication Guide reads:

> 3. LYRICA may cause swelling of your hands, legs and feet. This swelling can be a serious problem for people with heart problems.

FDA does not agree that this language must be deleted from the Medication Guide. This warning is stated in general terms and conveys the risk of swelling to patients without

[16] See supra n. 13.

explicit or implicit reference to any indication. Moreover, as you note in your petition, in section 6.1 of the LYRICA labeling, Table 5 ("Dose-related treatment-emergent adverse reaction incidence in controlled trials in adjunctive therapy for adult patients with partial onset seizures") specifically lists peripheral edema as an adverse reaction associated with the use of pregabalin for treating seizures (Petition at 12). This clearly indicates that the risk information related to peripheral edema was not solely derived from studies of LYRICA for treating pain.[17] The inclusion of this warning in the Medication Guide in no way reveals the omitted pain indications. Therefore, the warning is appropriately included, unchanged, in the Medication Guide for all pregabalin products, regardless of the indications for which they are approved.

III. CONCLUSION

We have reviewed your petition and other relevant information available to us. For the reasons stated above, we deny your request that FDA refrain from granting tentative or final approval for any ANDA for a generic version of LYRICA capsules if the ANDA includes proposed labeling that omits or carves out either LYRICA's seizure indication or LYRICA's pain indications. We have concluded that labeling changes necessary to accommodate carve-outs of LYRICA's patent-protected indications can be made and will not render the generic products less safe or less effective than LYRICA for the remaining approved indications.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[17] Even if the risk information were solely derived from pain studies, however, we do not believe that would prohibit its use in the labeling, so long as the indications protected by the applicable patent are not disclosed in the labeling.